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## **Independent predictors of early death of polytrauma patients: An analysis of 696 patients**

Mica, L ; Albrecht, K ; Keel, M ; Trentz, O

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## Independent Predictors of Early Death of Polytrauma Patients: An Analysis of 696 Patients

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### Abstract

Polytrauma patients are at high risk to die due to acute physiological deterioration after a high injury load within the first hours. Trauma scores such as ISS, NISS and APACHE II and laboratory parameters were collected at admission. The aim of this study was to evaluate the independent predictors of early death of the polytrauma patient.

A total of 696 patients (age  $40.8 \pm 15.5$  years) who had an ISS  $\geq 17$  and were admitted to a trauma center within the first 24 hours after trauma were included into this retrospective study. The patients were subdivided into survivors and those who died within the first 72 hours. ISS, NISS and APACHE II score, and laboratory parameters such as lactate, prothrombin time, pH-value, hematocrite, middle arterial pressure and platelets were collected at admission time. Data were compared with Mann-Whitney test and  $\chi^2$ -test for proportions. The data were considered as significant if  $p < 0.05$ . Predictive ability was evaluated by using receiver operating characteristic curves. Independent predictors were analyzed by logistic regression analysis.

Significantly increased values of ISS, NISS, APACHE II and serum lactate, and significantly decreased values of prothrombin time, middle arterial pressure, hematocrite, Platelets and pH-value were found in the non-survivor group ( $p < 0.001$ ). APACHE II, NISS, ISS score and the prothrombin time were found to be independent predictive values of death.

Early recognition of the risk of death followed by multidisciplinary resuscitation efforts could lead to a better survival rate in the population of polytrauma patients.

**Keywords:** Polytrauma; ISS; NISS; APACHE II; Prothrombin time

### Introduction

The availability of circulatory supportive medication and scheduled surgical strategies for the resuscitation of polytrauma patients led to a better survival outcome. Trauma scoring systems developed during the last decades define the threshold of a polytrauma but do not serve as predictive values of death. Independent predictors of an early death among the widely used trauma scoring systems and commonly available laboratory parameters such as lactate, pH, prothrombin time, platelets and hematocrite are not defined yet. The question still remains, which of the commonly used parameters are the most independent predictors of patients' early death after suffering a polytrauma. The aim is to improve resuscitative procedures and to prevent patient's early death as a multidisciplinary task.

Trauma scoring systems such as ISS, NISS, and APACHE II define the level of a polytrauma but do not serve as predictive values of early death. ISS and NISS describe the severity of trauma depending on the anatomical region and injury pattern. The injury pattern describes indirectly the severity of trauma, rendering the patient to higher risk of developing trauma associated diseases such as SIRS. APACHE II score uses different physiological and laboratory parameters at admission to describe the severity of the trauma load on the organism. However, all polytrauma patients are at high risk to develop an acute coagulopathy of trauma shock [1,2] in the first few hours after suffering the trauma. There [3] was a likelihood of 98% found to develop a coagulopathy if the ISS was above 25 points, the pH-value below 7.1, the core temperature under  $34^\circ\text{C}$  and the systolic blood pressure under 70 mmHg [3]. The traditional description depicts the acute coagulopathy of trauma shock [1] as a later event mainly caused by resuscitative attempts occurring in the hospital. There are patients admitted to the emergency room with

an already established or evolving coagulopathy due to trauma. Similar cases were reported in a retrospective study of 1088 [4] patients and confirmed by other retrospective studies with high case loads [5,6]. In these studies was a strong correlation between coagulopathy and mortality found, and coagulopathy was identified as an independent risk factor [4]. Acute coagulopathy of trauma shock was found to be associated with longer ICU stays [7], with higher risk to develop acute renal failure and multiple organ failure (MOF) [7] and with a trend towards acute respiratory distress syndrome [7]. In all these studies the transportation time was short and resuscitative fluid management was not excessive. Only few studies show the threshold values when to use blood products for resuscitation in the polytrauma patients and when to use normal saline [8] depending on ISS, NISS or APACHE II score. Independent predictors of the early death are not clearly defined, yet. Little is found in the literature showing clearly a benefit for survival after early and aggressive resuscitation with blood products in dependence of ISS, NISS or APACHE II score on one hand. On the other hand there seems to be a significant risk to develop an iatrogenic SIRS using blood-products for resuscitation as shown earlier [9]. This dilemma is

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not solved, yet, but the aim is clear: avoid death of the patient. An early identification of critically incipient trauma coagulopathy according to trauma scoring systems and laboratory parameters could lead to a lesser mortality and morbidity in the polytrauma patient.

In this study the focus was set on widely used trauma scoring-systems as a source for the severity of trauma and laboratory parameters as a sign of an early physiological deterioration. Commonly used laboratory parameters were analyzed which may guide physicians' decisions during the initial management of a polytrauma patient. The differences in clotting components, i.e. platelets, prothrombin time, the values of serum lactate and pH and whole blood parameters such as hematocrite and middle arterial pressure (MAP) were analyzed and compared with the values of survivors and non survivors over the first 72 hours. To provide useful information about the predictive value of widely used scoring systems, APACHE II, ISS and NISS scores were analysed. The aim was to determine independent predictive values of death within the first 72 hours of a polytrauma patient at admission.

## Materials and Methods

### Patients

696 polytrauma patients admitted to the emergency room of the University Hospital of Zürich in the time period of the year 1996-2002 were enclosed into this study. Admission criteria were an injury severity score (ISS)  $\geq 17$  points, age  $\geq 16$  years and an admission time at least 24h after suffering the polytrauma. The patients were subjected to intensive care treatment and damage control surgery. The population was subdivided into two groups: survivors and non survivors of the first 72 hours. All patients' data were collected retrospectively. ISS, NISS and APACHE II were defined according to the data collected at admission to the emergency department. All data were retrieved from patient's sheet according the local Institutional Review Board (IRB) approval according to the University of Zürich IRB guidelines and was conducted according to the guidelines of good clinical practice (*Retrospektive Analysen in der Chirurgischen Intensivmedizin* Nr. StV 01-2008).

### Surgical treatment

The treatment of all admitted patients followed the ATLS<sup>®</sup> guidelines and the previously assessed trauma-management protocol [10-12]. Briefly, after the airway, ventilation and cardiovascular management life saving surgery with decompression of body-cavities control of hemorrhage and contaminated tissue took place. The first surgical interventions were followed by stabilization of major fractures and radical debridement of death tissue. Cefazoline was used as peri-operative antibiotics. In all of the admitted patients an enteral nutrition was established within 24h after trauma to avoid spontaneous transmigration of the enteral microbial flora and peritoneal contamination.

### Trauma scoring systems

The Injury Severity Score (ISS) [13] and the New Injury Severity Score (NISS) [14] were used to define the severity of trauma. The Acute Physiology and Chronic Health Evaluation, APACHE II [15] score, was used to evaluate the overall physiological impairment of the patient.

### Laboratory parameters

Lactate, pH and hematocrite were measured in intervals with a blood-gas analyzer (ABL 800 Flex, Radiometer GmbH, Thalwil, CH). Platelets were measured by flow cytometry (FacsCalibur, Becton

Dickinson, Allschwil, CH). The prothrombin time was measured by a standardized previously described method [16].

### Statistical analysis

Continuous data are presented as mean  $\pm$  standard deviation (SD) and are compared between groups using the Mann-Whitney test. For proportions the  $\chi^2$ -test was used. All statistical computations were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Results were considered significant at  $p < 0.05$ . Predictive ability of variables was reported as area under the ROC-curve (AUC)  $\pm$  standard error. Independent predictors were analyzed by stepwise (forward and backward) logistic regression analysis.

## Results

### Patient population

Totally 696 patients with an average age of  $40.8 \pm 15.5$  years were included into this study. 528 were males and 168 were females. The overall admission time was  $2.0 \pm 1.9$  hours ( $2.1 \pm 2.2$  vs.  $1.6 \pm 0.9$ , survivor vs. non-survivor,  $p = 0.028$ ). Totally 184 (26.4% of all) patients died within the first 72 hours, 135 (27.6 % of males) males and 48 (28.4% of females) females (Table 1).

### ISS, NISS and APACHE II

The overall ISS of the admitted patients was  $35 \pm 12.6$  points and the overall NISS was  $43.6 \pm 12.3$  points (Table 1). The ISS ( $32.4 \pm 11.8$  vs.  $37.8 \pm 13.4$ , survivor vs. non-survivor,  $p < 0.001$ ) and NISS ( $41.4 \pm 13.5$  vs.  $50.2 \pm 14.1$ , survivor vs. non-survivor,  $p < 0.001$ ) scores were significantly elevated in the patients who did not survive the first 72 hours (Table 1). Similar predictive powers of ISS (AUC  $0.61 \pm 0.03$ ; Odds-Ratio 0.96) and NISS (AUC  $0.68 \pm 0.03$ ; Odds-Ratio 1.04) were found (Figure 1). APACHE II ( $15.2 \pm 7.9$  vs.  $25.3 \pm 7.7$ , survivor vs. non-survivor,  $p < 0.001$ ) score evaluated at admission was significantly elevated in patients who died within the first 72 hours (Table 1). A high predictive power (AUC  $0.80 \pm 0.02$ ; Odds-Ratio 1.15) of the APACHE II score was found at admission (Figure 1).

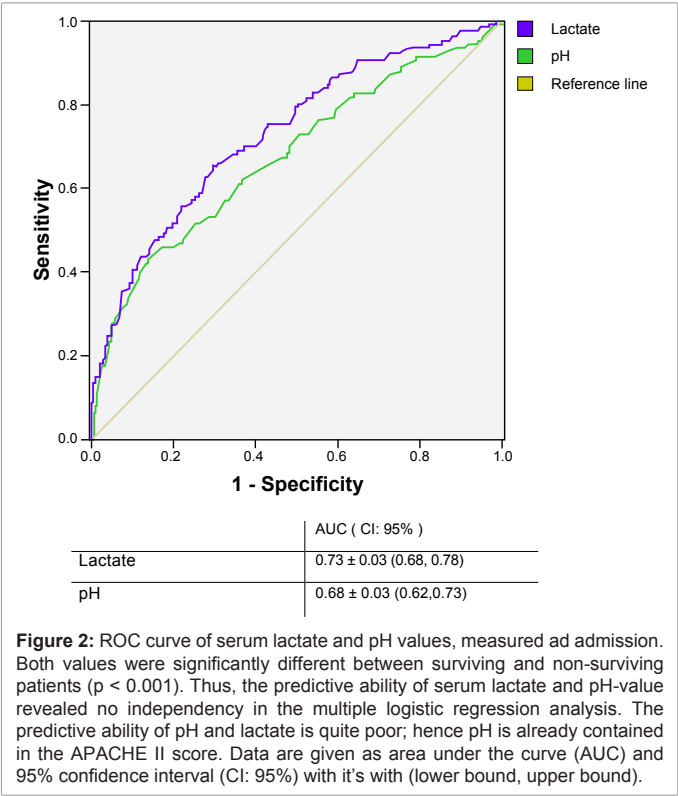
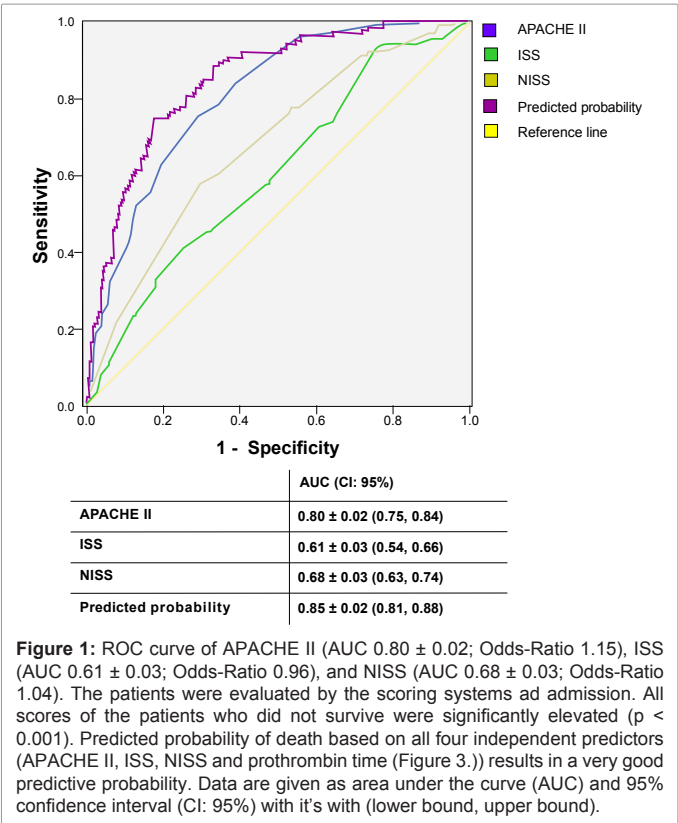
### Lactate acidosis at admission

Serum lactate ( $3.0 \pm 2.3$  vs.  $5.6 \pm 3.9$ , survivor vs. non-survivor,  $p < 0.001$ ) was evaluated at admission for each patient. The lactate values (AUC  $0.73 \pm 0.03$ ) (Figure 2) were significantly elevated in patients who did not survive the first 72 hours (Table 1). The serum

Characteristics	Survival over 3 days	Death within 3 days	p-value
Number [% of total]	512 (73.6%)	184 (26.4%)	ns. †
Age [years]	$39.1 \pm 16.6$	$45.5 \pm 19.2$	$< 0.001^*$
Males [% of Males]	393 (74.4%)	135 (27.6%)	ns. †
Females [% of Females]	121 (71.6%)	48 (28.4%)	ns. †
ISS [points]	$32.4 \pm 11.8$	$37.8 \pm 13.4$	$< 0.001^*$
NISS [points]	$41.4 \pm 13.5$	$50.2 \pm 14.1$	$< 0.001^*$
APACHE II [points]	$15.2 \pm 7.9$	$25.3 \pm 7.7$	$< 0.001^*$
Lactate [mmol/L]	$3.0 \pm 2.3$	$5.6 \pm 3.9$	$< 0.001^*$
pH	$7.31 \pm 0.13$	$7.2 \pm 0.2$	$< 0.001^*$
Platelets	$192 \pm 72.5$	$152 \pm 79.6$	$< 0.001^*$
Prothrombin Time [%]	$80.5 \pm 19.3$	$58.9 \pm 23.6$	$< 0.001^*$
Haematocrite	$33.4 \pm 7.8$	$26.4 \pm 79.6$	$< 0.001^*$
MAP	$93.2 \pm 37.1$	$79.7 \pm 30.0$	$< 0.001^*$
Admission time [h]	$2.1 \pm 2.2$	$1.6 \pm 0.9$	$0.028^*$

\*Mann-Whitney Rank Sum test, † $\chi^2$ -test.

**Table 1:** Characteristics of patient population (ISS: Injury Severity Score, NISS: New Injury Severity Score, APACHE II: Acute Physiology and Chronic Health Evaluation). Data are given as mean  $\pm$  SD, significance was set at  $p < 0.05$ , the data in parentheses are percentage values. \*Mann-Whitney test, † $\chi^2$ -test.



lactate concentrations were normalized after resuscitation and damage control surgery after 24 hours. There were no significant differences of lactate values found between groups after 24 hours. The pH values (7.31

± 0.1 vs. 7.2 ± 0.2, survivor vs. non-survivor, p < 0.001) (AUC 0.68 ± 0.03) (Figure 2) measured at admission were significantly reduced in patients who did not survive (Table 1).

Platelets and prothrombin time

Significantly decreased platelets (192 ± 75.5 vs. 152 ± 79.6, survivor vs. non-survivor, p < 0.001) (AUC 0.62 ± 0.03) and prothrombin times (80.5 ± 19.3 vs. 58.9 ± 23.6, survivor vs. non-survivor, p < 0.001) (AUC 0.76 ± 0.02; Odds-Ratio 0.98) (Figure 3) were found in patients who did not survive the first 72 hours (Table 1). After resuscitation and damage control surgery the values were mostly normalized without significant differences after 24 hours (data not shown).

Blood loss

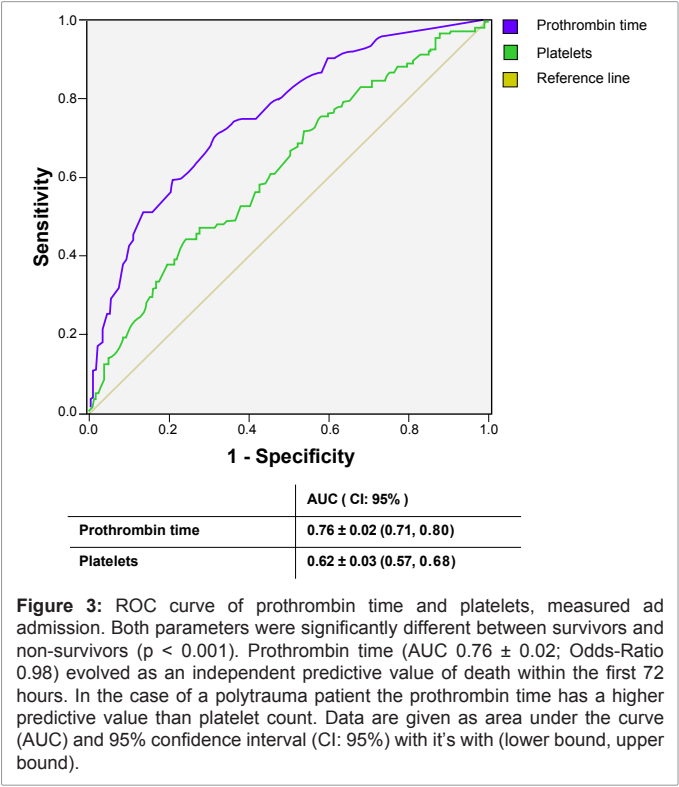
Haematocrite-values (33.4 ± 7.8 vs. 26.4 ± 7.9, survivor vs. non-survivor, p < 0.001) and middle arterial blood pressure (MAP) (93.2 ± 37.1 vs. 79.7 ± 30.0, survivor vs. non-survivor, p < 0.001) were measured at admission of the patients. As expected, these values were significantly (Table 1) reduced in patients who died within the first 72 hours (Haematocrite: AUC 0.64 ± 0.03, MAP: AUC 0.65 ± 0.03) (Figure 4).

Independent predictors of death: ISS, NISS, APACHE II and prothrombin time

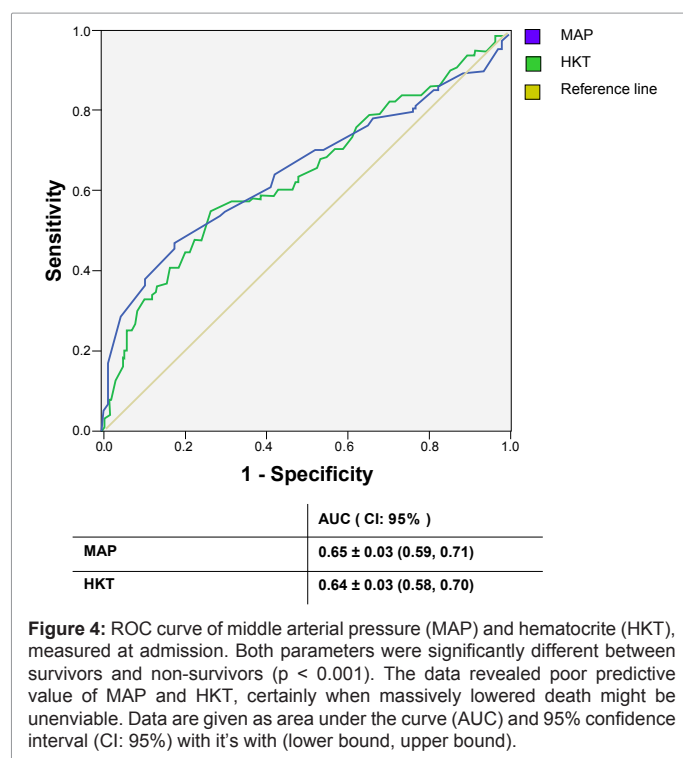
In a stepwise logistic regression including all significant parameters above, APACHE II, NISS, ISS score and the prothrombin time were found to be independent predictors of death. The combination “predicted probability” of these variables thus is a significantly better predictor than each single score (AUC 0.85 ± 0.02) (Figure 1)

Discussion

Massive bleeding is the key issue in trauma and emergency surgery







[17,18]. The availability of resuscitative components such as red blood cells, platelets and fresh frozen plasma does not guarantee the survival of a polytrauma patient with a massive hemorrhage after suffering a trauma. The data presented in this study show independent predictive parameters such as ISS, NISS, APACHE II and prothrombin time for the posttraumatic death within the first 72 hours after admission to a level I trauma center. Probably, pointing on decision guiding values. Normally, the operative mortality is low for most of the surgical interventions, ranging from  $< 0.1\%$  to  $8\%$  [19]. Unexpected acute bleeding during surgical interventions may raise the mortality over  $20\%$  [19]. Literature lacks clear evidenced procedures and independent predictive parameters to estimate the risk of early death and to avoid hemorrhage in polytrauma patients. This seems not to be very surprising due to the wide heterogeneity of this field.

### ISS and NISS: tissue destruction bleeds

Trauma leads to destruction of tissue and blood loss. The demonstrated data show significantly higher values in both scoring systems comparing the survival to the non-survival group, according to the severity of tissue destruction. Tissue destruction leads to the set free of the Kininogene and Kallikrein leading to the activation of the factor XII (Hageman-factor) [20]. Systemic spread of Kininogene and Kallikrein may activate systemically the factor XII leading to a consumptive coagulopathy. However, the mechanism how trauma coagulopathy develops remains uncertain. Other theories point on the rise of soluble thrombomodulin and fall in protein C levels after trauma [20]. This may be correlated with the development of acute coagulopathy of trauma shock [1]. Protein C is a natural anticoagulant excessively consuming plasminogen activator inhibitor (PAI-1) [20,2]. The correlation between rise of PAI-1 and decrease of protein C level were shown elsewhere [2]. Theoretically the increase in membrane-bound thrombomodulin on endothelial cells may lead to scavenging of thrombin, reducing its amount to produce fibrin and raising the

amount of activated protein C [21] and thus inhibiting the clotting cascade. However, these assumptions still remain speculative.

### APACHE II: physiological changes due to traumatic hemorrhage and tissue destruction

Metabolic lactate acidosis accompanied by hypothermia lowers the functionality of blood clotting factors supporting progressive bleeding. The activity of the prothrombinase complex (FXa/FVa) is reduced by  $50\%$  at pH 7.2, by  $70\%$  at pH 7.0 and by  $90\%$  at pH 6.8 [22,23]. Most of the factors involved in blood clotting are severely impaired in function when the pH is lower than 7.1: probably due to reduced affinity of  $\text{Ca}^{2+}$  binding sites. Hypothermia inhibits any enzymatic activity according to the equation of Arrhenius and van't Hoff and dilution during resuscitation and hypothermia favors ongoing bleeding. Hypothermia supports lactate acidosis by the above mentioned mechanism. Clinically significant changes in blood clotting are already observed at temperatures under  $34^{\circ}\text{C}$  ( $93.2^{\circ}\text{F}$ ) [23,24] even if the concentration of clotting factors has no pathological changes. When the core temperature falls below  $33^{\circ}\text{C}$  ( $91.4^{\circ}\text{F}$ ) in a polytrauma patient the activity of the blood-clotting system falls below  $50\%$  even if there is a normal factor concentration and functionality [24]. Higher APACHE II scores significantly increased the risk of death within the first 72 hours after admission. Early and aggressive resuscitative efforts with restoring patient's physiology especially blood coagulation and acidosis could improve the survival outcome.

### Acidosis

Lactate acidosis in the polytrauma patient roots in several problems: hypothermia, anemia and lactate acidosis itself. The kidney and the respiratory system usually fail to correct the acidosis in polytrauma and shocked patients. Corrective resuscitative interventions with e.g. sodium bicarbonate ( $\text{NaHCO}_3$ ) and tris-hydroxymethylaminomethane (THAM) may restore normal pH, furthermore, they seems to have a thrombo-permissive effect [25,26]. Acidosis increases the fibrinogen degradation by the factor 1.8 and thus leads to prolonged bleeding [27]. Parallely, the platelets are also inhibited by lower blood pH. However, how acidosis leads to decreased thrombocyte counts is not fully understood, yet. Transfusion of packed red blood cells may aggravate posttraumatic acidosis due to a lower base excess acquired during storage time [28]. There seems to be a general inhibition of all cellular functions during acidosis. Even when the pH-values reached a similar level after 24 hours the suppressive effect on physiological functions of acidosis could be long-termed.

### Platelets

There is evidence to keep platelet counts above  $50 - 100 \times 10^9/\text{L}$  in the polytrauma patient [29]. The shown platelet counts in this study show levels above  $100 \times 10^9/\text{L}$  also in patients who died within the first 72 hours after admission. Platelets and red blood cells have to be in a certain relation to allow optimal thrombocyte function. Thrombocyte function is reduced during acidosis with a permissive effect on ongoing bleeding. Thrombocytes measured after 24 hours (data not shown) had similar values in all groups pointing on a possible long-term effect, probably caused by acidosis. Platelet loss may be attributed to consumption at trauma site and to loss of whole blood.

### Prothrombin time

Significant reduction of the prothrombin time in patients who did not survive may be caused by hypothermia, acidosis and dilution or activation-decay [30]. The main reason for the reduction of the values

cannot be identified here. The acidosis correlates with the reduction of the prothrombin time, as discussed earlier. Dilution of the blood coagulation cascade during resuscitative attempts has not to be considered due to very low rescue-times and low resuscitative volumes of cristaloids. Further more, the loss of whole blood and acidosis seem to be the core reasons for reduced prothrombin times and for the independence as a predictor of death.

## Hematocrite

The decreased hematocrite values favor the development of acidosis. Lowered haematocrite is a double cutting edge, it favors hypoxemia and an anaerobic metabolism resulting in lactate acidosis and the reduction of haemoglobin reduces also the main blood buffer system [31]. The data shown in this study suggest hemorrhage as a death factor. Taken to gather lower hematocrite-values favor the genesis of lactate acidosis [31], acidosis itself inhibits the blood coagulation cascade and probably also the normal function of platelets. There is evidence that early and aggressive resuscitation with FFP (fresh frozen plasma) and red blood cells (RBC) improves the ICU outcome of the polytrauma patient [32,33]. The very early normalization of the blood-clotting pathway could lead to a better survival ratio as seen in military trauma settings [33].

## Conclusions

The APACHE II, ISS and NISS scores with the prothrombin time as independent predictive values of death can be used to guide surgeons' decisions during the management of an acute polytrauma patient. This data show that the very early management of polytrauma patient, according to the independent predictive factors could improve the outcome of the polytrauma patient. This proves the 'golden hour' in the treatment of trauma shock.

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